Please remove pages 1-4 of the Sequence Listing and replace with enclosed pages 1 to 114 which constitute the entire Sequence Listing. The substitute computer readable form of the sequence listing is the same as the substitute paper copy of the sequence listing. The new sequence information provided in the Specification is also the same as the sequence listing of the enclosed substitute computer readable and paper forms of the sequence listing. Applicants submit that due to the citation to the accession numbers in the application, no new matter is added with the addition of these sequences.

In the Claims:

Please cancel claims 9, 16 and 18-26 without prejudice or disclaimer.

Please amend the claims as follows:

1. (amended) A method for screening for an increased risk of hypercalciuria comprising:

(a) obtaining a sample nucleic acid from a subject; and

(b) analyzing the sample nucleic acid to detect the presence or absence of a genetic mutation in a genomic region associated with an increased risk of developing hypercalciuria, wherein said genomic region is comprised in chromosome 1q23.3-1q24.

12. (amended) The method of claim 1, wherein the genomic region has a sequence contained in at least one genetic sequence selected from the group consisting of the the genetic sequences set forth in GenBank Accession # Z97876 (SEQ ID NO. 7, SEQ ID NO. 8 and SEQ ID NO. 9), GenBank Accession # Z99943 (SEQ ID NO. 10), and GenBank Accession # AL031733 (SEQ ID NO. 7).

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-26 were pending at the time of the present action. Of these, claims 16 and 18-26 have been canceled. Claims 1-15 and 17 were rejected by the Action. Claim 1 and 12 have been amended. Therefore, claims 1-15 and 17 are currently pending. These claims, as currently pending, are reproduced in Appendix A.

B. Summary of the Interview with the Examiner Robinson

On September 27, 1999, Applicants' representative, Mark B. Wilson, conducted an interview with Examiner Robinson. During this conversation, a provisional election was made without traverse to prosecute the invention of claims 1-15 and 17 drawn to a method for screening for increased risk of hypercalciuria. Applicant's confirm the election and have canceled claims 16 and 18-24.

C. The Action Improperly Fails to Accord the Application the Provisional Filing Date

The Action asserts that the Applicants have "not complied with one or more conditions for receiving the benefit of an earlier filing date." The Action contends that the application will be provided with the filing date of the present application because "the Examiner read the provisional application and did not find support for sequences recited in the claims and disclosed in the specification" and "the marker D1S2681 wherein the genomic region of the invention is comprised." Applicants respectfully traverse this allegation.

While additional material was provided when the provisional application was converted to the instant application, the provisional application was nonetheless adequate to enable the instant invention. The provisional application provides a disclosure of "the identification of a

region on human chromosome 1 located between 1q23 and 1q24 that contains a region associated with an increased risk of AH (page5, line 21)." The disclosure further discloses how the region was localized (page 107, line 18 *et seq.*) and provides teaching of how this information, when combined with the knowledge of one of ordinary skill in the art would facilitate screening of at risk individuals (page 54, line 11 *et seq.*). The Action does not provide any evidence refuting why the disclosure included with the provisional is inadequate to accord priority to the full scope of the invention as claimed. Of course, this is not an issue at this time because no rejection based upon prior art has been asserted.

D. The Action's Rejections under 35 U.S.C. §112, First Paragraph, are Overcome

The Action rejects claims 1-15 and 17 under 35 U.S.C. §112, first paragraph, asserting that the specification fails to adequately enable the scope of the claims as presently drafted. The Action argues that, while the specification is enabling for claims related to the nucleic acid sequence contained in SEQ ID NO. 1, it does not reasonably provide enablement for any hypercalciuria gene. Applicants respectfully traverse this rejection.

It is well established that a rejection based on a lack of enablement must be supported. For example, the court in *Gould v. Mossinghoff*, 229 USPQ 1 (D.C. 1985) stated:

> In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971).
>
> The PTO thus must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982). [Emphasis supplied.]

The application localizes the region of a genetic defect which evidence clearly indicates is related to the development of AH in certain individuals. The Action fails to carry its burden of establishing that this information in combination with the additional guidance provided by the specification and the knowledge of one of ordinary skill would be inadequate to enable the full scope of the claims. The Action has erroneously placed the burden of proof on Applicants without offering any evidence or reasoning based on the record as a whole why the disclosure is not enabling for using the disclosed information to screen for similar defects in other individuals. The majority of the "grounds" of rejection were speculations without support. If the rejection is to be maintained, the Examiner must support this position by citing published references or by Examiner's Affidavit, as required by MPEP 2144.03. In the absence of this support, this rejection cannot stand.

While the Action provides elements based upon *Ex parte Forman* attempting to establish the lack of proper enabling disclosure, these arguments are inadequate to carry the required burden in light of the claims as presently pending. The elements are specifically addressed as follows:

1) *Experimentation would not be undue in light of the provided disclosure*:

A person of ordinary skill could readily develop methods of screening for defects within the disclosed region. In its simplest form, hybridization assays, while time consuming, would screen for specific defects within an individual. RNase protection and DDGE would provide further, more technical methods for making such determinations. It would not require undue effort or experimentation to apply the knowledge of a person of ordinary skill to implement such methods of screening.

2) *The amount of direction or guidance provided by the specification is adequate*:

The Action asserts that inadequate direction or guidance is provided by the specification. The Action, however, fails to provide any evidence of this deficiency as required by *Gould.* As previously argued by Applicants, the disclosure provides adequate information, which, when combined with the knowledge of one of ordinary skill would allow for the screening for inherited defects potentially leading to AH.

3) *Adequate working examples are provided:*

The Action asserts that the single working example is inadequate. An application need not include working examples in order to be enabled. Nevertheless, the '352 specification includes a working example and sets forth the screening technique that led to the determination that the region of interest was linked to AH. Absent evidence from the PTO that these working examples are inadequate, the Action is in error in asserting that this is grounds for supporting this §112 rejection.

4 & 6) *The nature of the invention and unpredictability of the art does not obviate the PTO's burden:*

While the relevant art of the subject matter of the invention is considered unpredictable by the PTO, the PTO must still meet is burden of providing adequate evidence that the specification is not in fact enabling for the scope of the claims. The Action fails to offer evidence that the teachings of the disclosure are, in fact, inadequate.

5) *The state of the prior art and relative skill do not create the presumption that the scope of the claims in not enabled*:

While the skill in the art necessary to localize a genetic defect to a specific region is relatively high, once it is known that the defect is localized in a region, the skill necessary

to capitalize upon this information and use the information in a screening assay is much less. RNase protection and DGGE techniques do not require the technical expertise required to make the initial identification and localization. The prior art available for techniques adequate for screening is well developed and readily within the skill of the individual to which this application is directed.

7) *The claims as presently pending are commensurate with the enablement provided by the specification*:

As previously argued, the specification provides teaching sufficient to enable one of ordinary skill in the relevant art to make the invention claimed.

Notwithstanding the Actions failure to properly carry its burden for establishing an enablement rejection, the scope of the claims is adequately enabled by the Applicants' disclosure.

The '352 application's specification provides sufficient evidence that inherited hypercalcuria is, in some individuals, linked to an inherited defect in the 1q23.3-1q24 region of chromosome 1. The Applicants successfully established, through linkage analysis that a genetic defect exhibited by three unrelated, effected kindred localized to the q arm of chromosome 1 at 1q23.3q-q24. Based upon this information, it would not require undue experimentation to derive a means of screening individuals for an enhanced risk of AH based upon a similar genetic defect. Techniques would clearly be within the purview of a person of ordinary skill to readily develop screening techniques based upon this disclosure for determining whether individuals are genetically predisposed to developing AH. Further, the specification provides teaching related to how such methods could be derived including means of eliciting specific defects within the region (see, for example 58 line 20 *et. seq*) as well as sequence information for areas within the

disclosed region (see, for example SEQ ID NO.s 1-11). One of ordinary skill would recognize that the disclosure provides adequate information such that assays could be developed employing techniques to detect specific inherited defects indicative of a genetic predisposition for AH (for example, RNase protection or DGGE as discussed in the specification at pg. 58 line 20 *et. seq.*).

Based upon the knowledge of one of ordinary skill in the relevant art, it would not require undue experimentation to use the loci and sequence information provided by the Applicants to screen for specific defects within the 1q23.3q-q24 region of chromosome 1. In light of these arguments, it is felt that the rejection of claims 1-15 and 17 is no longer proper. Withdrawal of the rejection is therefore respectfully requested.

E. The Actions Rejections under 35 U.S.C. §112, Second Paragraph, are Overcome

The Action rejects claim 12 under 35 U.S.C. §112, second paragraph, as being indefinate. The Action asserts that the failure to include SEQ ID information for the genetic sequences as set forth by GeneBank accession numbers Z97876, Z99943, and AL031733 make claim 12 indefinite. One of ordinary skill, would be able, based upon the inclusion of the accession numbers to access the relevant sequences. Nevertheless, the specification has been amended to include sequence information for the cited matter in order to expedite prosecution of this matter. Because the accession numbers were incorporated by reference in the specification, it is asserted that this amendment results in the inclusion of no new matter.